**Supplementary material**

***Effects of intraoperative fluid management during liver transplantation on postoperative acute kidney injury: an observational cohort study.***

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# **Appendix I – Local intraoperative transfusion guidelines**

Red blood cell transfusions were used when cellsaver output was insufficient to compensate blood loss and/or when hemoglobin concentration was below a certain threshold. Hemostatic blood products were used to treat significant bleeding and not as a prophylaxis to correct abnormal laboratory values. We used only classic central laboratory coagulation tests to guide our coagulation management.

Our transfusion thresholds were the following for each blood product:

* Red blood cells: hemoglobin value between 60 and 70 g/L
* If intraoperative overt bleeding is observed:
  + Fresh frozen plasma (10 to 15 ml/kg): INR > 1.5
  + Platelets (5 to 10 units): platelet count ≤ 30 × 109/L
  + Cryoprecipitate (5 to 10 units): fibrinogen ≤ 2 g/L

# **Appendix II – Selection of covariates**

We chose covariates based on their hypothesized association with both exposure and outcomes, outside of the causal pathway, and based on the published literature. (1-9) A consultation with local experts was conducted among the anesthesiologists performing liver transplantation in our center. The objective was to identify fluid management interventions performed by anesthesiologists as well as variables that might influence these interventions. All fluid management interventions reported by anesthesiologists were captured by all the components of our defined exposure, including the volume of drained ascites and intraoperative bleeding. Volume of ascites has already been associated with postoperative acute kidney injury (2) and we thought it might be a surrogate marker of portal hypertension severity and influence intra-operative need for fluid administration. Intraoperative bleeding has an obvious association with the volume of fluid received and has already been associated with acute kidney injury (AKI).

According to the consultation results and the clinical insight of the investigators based on published data in this population, the following main covariates seemed to be potential confounders: hemodynamic instability, high doses of vasopressors, phlebotomy, preoperative renal failure and anemia, intraoperative signs of hypervolemia, CVP, heart failure and severe coagulopathy. Some of these variables have already been associated with our outcome of interest in previous studies, which emphasizes their role as potential confounders. Severity of liver disease (MELD-NA) has already been associated with worse postoperative outcomes and an increased risk of acute kidney injury.(5) Severity of liver failure will also be evaluated by the inclusion of acute liver failure as the transplantation indication. We hypothesized that coagulopathy would be captured by the MELD-Na. However, since our primary outcome is AKI and has been highly reported by anesthesiologists to influence their practice, we decided to add the preoperative creatinine value as a potential independent confounder, as well as preoperative diabetes status. Pre-operative hemoglobin level and the use of phlebotomy has also been associated with the risk of bleeding and transfusions. (10) Baseline CVP might be a surrogate marker of both the patient’s volume status and heart function status, has been used to control fluid infusion in some studies (11) and also, by itself, affects the fluid strategy used intraoperatively in our center. Heart failure was reported to be a baseline comorbidity that might affect the fluid strategy used by anesthesiologists. However, a recent transthoracic echocardiogram is not always available in our center. Therefore, we decided to include only the CVP as a potential confounder, since it has been recently associated with intraoperative bleeding and transfusions in a local 800 patient cohort.(4,5,9,12) Post-reperfusion syndrome is a vasoplegic shock after transplantation that is associated with renal failure and could by a significant confounder. (13). We added the cold ischemia time, because of its association with the postreperfusion syndrome and the potential confounding effect on the need for more fluid resuscitation. Finally, we added the length of vena cava clamping, because this surgical intervention might increase the need for fluid resuscitation to maintain hemodynamic stability and could be associated with AKI. We did not include measures of hemodynamic instability or vasopressor doses used as potential confounders because we believe part of this item is within the causal pathway between the exposure and our primary outcome. The differential effects of vasopressors and fluid management, their interaction and the mediation effect between them will nonetheless have to be explored in another study.

# **Appendix III – Supplementary information on data sources, measurement and management**

Demographic characteristics, liver disease diagnosis, intraoperative volume of fluid received, intraoperative bleeding, urine output, type of fluid used (crystalloids, synthetic colloids, albumin, cellsaver output, RBC and other blood products), performance of a phlebotomy, baseline central venous pressure value (CVP) and preoperative hemoglobin levels were already available in databases used for either anesthesia research or clinical follow-up. Exclusion criteria (combined transplantations and preoperative dialysis status), baseline comorbidities, severity of liver failure (MELD-Na), preoperative creatinine and postoperative creatinine levels and diuresis, volume of drained ascites, cold ischemia time (CIT), vena cava clamping time and type, postoperative blood products transfusions up to 48 hours, time to first extubation, ICU discharge and death date (or last time seen alive) were extracted from patients’ chart. 30-day, 180-day and 1-year creatinine clearance outcome were available in one of the databases; for missing MDRD values, creatinine values were used to calculate it.

Administered fluid, transfused blood products, estimated blood loss and intraoperative urine output were prospectively collected by anesthesiologists using a standardized case report form since 2002 and transferred to a local anesthesia database. For this study, we merged this anesthesia database with the database managed by hepatologists that included perioperative data. We extracted from charts all other needed variables. The only variable included in our fluid balance exposure that had to be retrospectively extracted was ascites. We used the value reported by the surgeon or the operating room nurse in their reports. For missing ascites on these reports, we extracted semi-quantitative values (or absence of ascites) from radiological reports of abdominal imaging that preceded the transplantation by less than 6 months. Mild, moderate and severe ascites were imputated with a 500 ml, 1500 ml or 5000 ml value respectively (clinical decision, median, 75e percentile respectively). At the end, 98 ascites values were still missing. Blood products were considered to have the following volume, based on the mean volume received by our blood bank: 305 ml for red blood cells, 250 ml for fresh frozen plasma, 70 ml for each unit of platelets and 20 ml for each unit of cryoprecipitates. Baseline CVP was the first measured CVP after insertion of the central line in the operating room and used as a surrogate variable of volemia. Transesophageal echocardiography values were not available since it was used only in very selected cases.

We calculated MELD-Na with laboratory values closest to surgery according the 2016 UNOS recommendations, but without censoring values above 40 as performed for transplantation prioritization. We considered both primary acute liver failure and graft dysfunction as acute liver failure for the analyses. Extubation associated with an end of active care or palliative transfer to the ward was classified as death. Date of death was extracted from patients’ charts and the date of last visit seen alive was used as censor if the patient was lost to follow-up during the first postoperative year.

One author (LLC) extracted all data from selected charts. Another author (FMC) double extracted the first 20 charts as well as 5 random charts among the 100 first ones to calibrate and validate data extraction. All unclear data in the chart were identified by queries and reextracted. Extracted data from patients’ chart was coded in an electronic database using the Research Electronic Data Capture (REDCap) platform hosted by the Research Center of the Centre Hospitalier de l’Université de Montréal (CRCHUM). Data from our ancillary databases was subsequently merged with the manually extracted data. Access was protected by passwords and only participating researchers were able to access the data.

# **Appendix IV – Sample size calculation**

Output from The SAS system.

The POWER Procedure

Likelihood Ratio Chi-Square Test for One Predictor

| **Fixed Scenario Elements** | |
| --- | --- |
| **Method** | Shieh-O'Brien approximation |
| **Alpha** | 0.05 |
| **Response Probability** | 0.25 |
| **Test Predictor** | Main |
| **Unit for Test Pred Odds Ratio** | 250 |
| **Nominal Power** | 0.8 |

| **Computed N Total** | | | | | |
| --- | --- | --- | --- | --- | --- |
| **Index** | **Test OR** | **Covariates** | **Total N Bins** | **Actual Power** | **N Total** |
| **1** | 1.05 | Creat | 100 | 0.801 | 451 |
| **2** | 1.05 | Hb | 100 | 0.801 | 451 |
| **3** | 1.05 | Meld | 350 | 0.801 | 451 |
| **4** | 1.05 | Colloid | 100 | 0.801 | 451 |
| **5** | 1.05 | Alb | 100 | 0.801 | 451 |
| **6** | 1.05 | Phlebo | 30 | 0.801 | 451 |
| **7** | 1.05 | Ascite | 100 | 0.801 | 451 |
| **8** | 1.05 | TVC | 100 | 0.801 | 451 |
| **9** | 1.05 | Saignement | 100 | 0.801 | 451 |
| **10** | 1.05 | clamp | 100 | 0.801 | 451 |
| **11** | 1.05 | ischemie | 100 | 0.801 | 451 |
| **12** | 1.10 | Creat | 100 | 0.802 | 110 |
| **13** | 1.10 | Hb | 100 | 0.802 | 110 |
| **14** | 1.10 | Meld | 350 | 0.802 | 110 |
| **15** | 1.10 | Colloid | 100 | 0.802 | 110 |
| **16** | 1.10 | Alb | 100 | 0.802 | 110 |
| **17** | 1.10 | Phlebo | 30 | 0.802 | 110 |
| **18** | 1.10 | Ascite | 100 | 0.802 | 110 |
| **19** | 1.10 | TVC | 100 | 0.802 | 110 |
| **20** | 1.10 | Saignement | 100 | 0.802 | 110 |
| **21** | 1.10 | clamp | 100 | 0.802 | 110 |
| **22** | 1.10 | ischemie | 100 | 0.802 | 110 |
| **23** | 1.15 | Creat | 100 | 0.803 | 49 |
| **24** | 1.15 | Hb | 100 | 0.803 | 49 |
| **25** | 1.15 | Meld | 350 | 0.803 | 49 |
| **26** | 1.15 | Colloid | 100 | 0.803 | 49 |
| **27** | 1.15 | Alb | 100 | 0.803 | 49 |
| **28** | 1.15 | Phlebo | 30 | 0.803 | 49 |
| **29** | 1.15 | Ascite | 100 | 0.803 | 49 |
| **30** | 1.15 | TVC | 100 | 0.803 | 49 |
| **31** | 1.15 | Saignement | 100 | 0.803 | 49 |
| **32** | 1.15 | clamp | 100 | 0.803 | 49 |
| **33** | 1.15 | ischemie | 100 | 0.803 | 49 |
| **34** | 1.20 | Creat | 100 | 0.810 | 29 |
| **35** | 1.20 | Hb | 100 | 0.810 | 29 |
| **36** | 1.20 | Meld | 350 | 0.810 | 29 |
| **37** | 1.20 | Colloid | 100 | 0.810 | 29 |
| **38** | 1.20 | Alb | 100 | 0.810 | 29 |
| **39** | 1.20 | Phlebo | 30 | 0.810 | 29 |
| **40** | 1.20 | Ascite | 100 | 0.810 | 29 |
| **41** | 1.20 | TVC | 100 | 0.810 | 29 |
| **42** | 1.20 | Saignement | 100 | 0.810 | 29 |
| **43** | 1.20 | clamp | 100 | 0.810 | 29 |
| **44** | 1.20 | ischemie | 100 | 0.810 | 29 |

**Supplemental information on sample size**

Our sample size calculation used mean crystalloid volume of 4 ± 1.5 L as the main independent variable, since all components of our fluid balance exposure was not available at that time. Our sample size was estimated at 500 patients. Due to chart access problems, we realized, before the end of the extraction, that some charts between July 2008 and December 2010 were missing from our list. We extracted these charts before any data analysis to ensure a cohort of consecutive transplantations, which inflated our sample size by 28 patients up to 528 patients.

# **Appendix V – Supplementary information on missing data and statistical analyses**

Our exposure variable summarized blood volume state into one single variable, which reduced the number of variables included in a multivariable model and helped managed potential multicollinearity between administered fluid, transfused blood products and blood losses. We had 105 missing data for fluid balance (98 because of missing ascites), 49 for 48-hour diuresis and 185 for 7-day diuresis that were handled by multiple imputations for all main analyses. We evaluated the effects of the assumptions underlying multiple imputations by sensitivity analyses.

All analyses were multivariate models adjusted for the same potential confounders (age, gender, diabetes, MELD, preoperative creatinine and hemoglobin value, acute liver failure, retransplantation, baseline CVP, type and length of vena cava clamping, CIT, exposure to starch and phlebotomy). However, we limited covariates for the RRT model and survival model because only 31 and 40 events occurred respectively. For the RRT model, we included fluid balance, age, gender and significant variables from the 48-hour and 7-day models: MELD, cold ischemia time and baseline creatinine concentration. This included one variable per 5.1 event. For the survival model, we included variables known to be associated with postoperative mortality in previous literature as well as our exposures of interest: fluid balance, intraoperative phlebotomy, age, retransplantation, MELD, ALF as well as a propensity score using variables that are associated with an intraoperative phlebotomy based on the local clinical practice (baseline hemoglobin and creatinine values, as well as baseline CVP at the start of surgery; see appendix II, table S1) and an interaction term between time and ALF (see below). This included one variable per 5 events. We explored interaction between phlebotomy and our main exposure, fluid balance, in all models.

We fitted all models according to the distribution of the dependent variable. We fitted the linear or generalized linear models by generalized estimating equations (GEE) using robust standard errors with an exchangeable correlation matrix to account for within-patient correlation. We fitted multivariate marginal proportional competing risk models for time to first extubation and time to ICU discharge using Fine and Gray cumulative incidence curves derivates (death being considered a competing censoring mechanism) and a multivariate marginal proportional Cox model for survival up to 1 year. We used robust standard errors to consider within-patient correlation for all marginal time-to-event models.

We verified the linear relationship in the linear regression models by a visual residual analysis. We explored non-linear relationship between our main exposure and outcomes in all models; non-linear models were only significant in our competing risk models for time to extubation and time to ICU discharge. The relation between fluid balance and time to event was best fitted by 3-node restricted cubic splines for the two models. The effect of fluid balance from these models was estimated from a visual analysis of the fluid balance dependent hazard ratios presented in figures 3 and S3. We performed a likelihood ratio test to assess the statistical significance of this association. For these two models, we also explored the interaction between a phlebotomy and the spline terms and evaluated the significance of the effect with a likelihood ratio test between the additive and the interaction model. Interaction was significant only in the time-to-extubation model. To express the observed effect, we fitted models in patients with a phlebotomy and in patients without a phlebotomy and produced a fluid-dependent hazard ratio curve for the two models.

We tested the proportionality assumption for all significant variables in our proportional odds models and this assumption was respected. In our time-to-event models, we explored model’s proportionality assumption by Schoenfeld residuals visual analysis and by the Harrel and Lee goodness-of-fit test; this assumption was not respected for any model, both for the overall model and the main exposure. The assumption was respected when we added strata for starch exposure in the time-to-extubation and time-to-ICU discharge models and strata for hemoglobin in the time to extubation model. For the survival model, we added a linear interaction term between ALF and time that was significant and solved most of the proportionality assumption problem. The time-dependent HR for ALF may be expressed as = . A slight proportionally assumption problem was also detected for the main exposure; however, the interaction term with time solved the problem but was not clinically meaningful.

Survival curves were not produced from the models fitted on imputated datasets. They were produced from fitted models from the complete case only dataset, without strata and time interaction, and with a tertile-based categorization of the main exposure to obtain visual meaningful curves.

Finally, our main exposure was an aggregated variable of administered volume of crystalloids, colloids, cellsaver output and blood products and lost volume of blood, ascites and urine. The use of such a variable was based on many *a priori* considerations, one of them being the management of potential multicollinearity. We calculated *a posteriori* Pearson coefficient between administered products and blood losses on the complete dataset to explore the relation between these variables. We found a correlation of 0.53 between volume of administered fluid and blood losses and a correlation of 0.72 between volume of administered fluid + blood products transfused and blood losses; these correlations confirmed potential multicollinearity problems. However, we did not find any collinearity in our final models using the VIF statistics.

# **Appendix VI – Supplementary tables and figures**

**Table S1. KDIGO-AKI criteria**

|  |  |  |
| --- | --- | --- |
| **Stage** | **Serum creatinine** | **Urine output** |
| 1 | 1.5–1.9 times baseline OR  ≥ 26.5 mmol/l increase | < 0.5 ml/kg/h for 6–12 hours |
| 2 | 2.0–2.9 times baseline | < 0.5 ml/kg/h for ≥ 12 hours |
| 3 | 3.0 times baseline OR  Increase in serum creatinine to ≥ 353.6 mmol/l OR  Initiation of renal replacement therapy OR | < 0.3 ml/kg/h for ≥ 24 hours OR  Anuria for ≥ 12 hours |

**Table S2. Exploratory univariate analyses for 48-hour AKI**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **POR** | **CI** | **p value** |
| Fluid balance (L) | 0.97 | [0.93, 1.01] | 0.172 |
| Total administered fluid volume (L) | 0.97 | [0.89, 1.05] | 0.426 |
| Ascites (L) | 1.04 | [0.99, 1.10] | 0.086 |
| Blood loss | 1.07 | [0.94, 1.21] | 0.300 |
| Gender (male) | 0.90 | [0.64, 1.25] | 0.515 |
| Age | 1.02 | [1.01, 1.04]\* | 0.001 |
| Retransplantation | 0.43 | [0.26, 0.72]\* | 0.001 |
| ALF | 1.17 | [0.55, 2.49] | 0.681 |
| MELD | 1.04 | [1.02, 1.06]\* | < 0.001 |
| Diabetes | 1.27 | [0.85, 1.91] | 0.244 |
| Baseline CVP (mmHg) | 1.02 | [0.99, 1.05] | 0.255 |
| CIT (hours) | 1.06 | [0.99, 1.13] | 0.058 |
| Vena cava clamping time (minutes) | 1.01 | [0.99, 1.01] | 0.236 |
| Baseline hemoglobin (g/L) | 0.99 | [0.99, 1.00] | 0.067 |
| Baseline creatinine (10 μmol/L) | 1.00 | [0.96, 1.03] | 0.900 |
| Intraoperative phlebotomy | 1.04 | [0.77. 0.57] | 0.088 |
| Piggyback | 0.70 | [0.32, 1.51] | 0.357 |
| Starch exposure | 1.22 | [0.89, 1.66] | 0.211 |

*On complete cases only.*

*\* Statistically significant*

*POR= proportional odds ratio, CI = confidence interval, ALF = acute liver failure, CVP = central venous pressure, CIT = cold ischemia time*

**Table S3. Creatinine clearances**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **30 days ()**  **(n=510)** | **180 days ()**  **(n=495)** | **365 days ()**  **(n=485?)** |
| Fluid balance (L) | -0.54 [-1.39, 0.30] | 0.33 [-0.34, 1.00] | 0.30 [-0.34, 0.93] |
| Age | -0.75 [-1.01, -0.50]\* | -0.71 [-0.95, -0.48]\* | -0.73 [-0.95, -0.51]\* |
| Gender (male) | 8.48 [3.76, 13.20]\* | 6.23 [2.17, 10.29]\* | 5.67 [1.72, 9.62]\* |
| Retransplantation | -2.51 [-9.95, 4.92] | -3.07 [-10.47, 4.31] | 0.70 [-6.86, 8.25] |
| ALF | 5.89 [-2.31, 14.10] | -1.53 [-9.69. 6.64] | -7.62 [-15.95, 0.71] |
| MELD | 0.09 [-0.34, 0.50] | 0.11 [-0.22, 0.44] | 0.19 [-0.14, 0.52] |
| Diabetes | -4.99 [-9.88, -0.10]\* | -1.89 [-5.69, 1.91] | -1.96 [-6.35, 2.43] |
| Baseline CVP (mmHg) | -0.49 [-0.88, -0.11]\* | -0.34 [-0.66, -0.02]\* | -0.41 [-0.73, -0.10]\* |
| CIT (hours) | -0.25 [-1.20, 0.69] | -0.14 [-0.87, 0.59] | -0.18 [-0.95, 0.58] |
| Vena cava clamping time (minutes) | -0.09 [-0.18, -0.01]\* | -0.02 [-0.11, 0.06] | -0.02 [-0.09, 0.05] |
| Baseline hemoglobin (g/L) | 0.02 [-0.10, 0.14] | 0.14 [0.05, 0.24] \* | 0.16 [0.06, 0.27]\* |
| Baseline creatinine (10 μmol/L) | -1.47 [-2.07, -0.86]\* | -1.46 [-1.99, -0.92]\* | -1.38 [-1.93, -0.83]\* |
| Intraoperative phlebotomy | 0.06 [-4.68, 4.80] | -3.61 [-8.04, 0.83] | -3.14 [-7.82, 1.54] |
| Piggyback | 3.66 [-7.28, 14.59] | 6.36 [-3.16, 15.88] | -3.66 [-11.28, 3.96] |
| Starch exposure | -1.42 [-5.58, 2.75] | -6.42 [-9.73, -3.10]\* | -5.39 [-8.78, -2.01]\* |

*= fitted regression coefficient, ALF = acute liver failure, CVP = central venous pressure, CIT = cold ischemia time*

**Table S4. Postoperative red blood cell transfusions**

|  |  |
| --- | --- |
| **Variables** | **Multiplicative factor**  **(n=527)** |
| Fluid balance (L) | 1.01 [0.96, 1.06] |
| Age | 0.99 [0.98, 1.00] |
| Gender (men) | 0.83 [0.60, 1.16] |
| Retransplantation | 1.10 [0.61, 1.99] |
| ALF | 0.88 [0.43, 1.82] |
| MELD | 1.05 [1.01, 1.09]\* |
| Diabetes | 0.79 [0.42, 1.46] |
| Baseline CVP (mmHg) | 1.02 [0.98, 1.05] |
| CIT (hours) | 1.06 [0.98, 1.15] |
| Vena cava clamping time (minutes) | 1.00 [1.00, 1.01] |
| Baseline hemoglobin (g/L) | 1.00 [0.98, 1.01] |
| Baseline creatinine (10 μmol/L) | 1.01 [0.98, 1.04] |
| Intraoperative phlebotomy | 0.69 [0.42, 1.14] |
| Piggyback | 1.89 [0.89, 4.01] |
| Starch exposure | 1.15 [0.82, 1.62] |

*ALF = acute liver failure, CVP = central venous pressure, CIT = cold ischemia time*

**Table S5. Time to first extubation**

|  |  |
| --- | --- |
| **Variable** | **Extubation (HR)**  **(n=526)** |
| Fluid balance | 1.00 [0.96, 1.04] |
| Intraoperative phlebotomy | 1.04 [0.80, 1.35] |
| Age (years) | 1.00 [0.99, 1.01] |
| Gender (male) | 1.33 [1.02, 1.74]\* |
| Retransplantation | 1.00 [0.63, 1.59] |
| ALF | 0.47 [0.22, 0.98]\* |
| MELD | 0.98 [0.96, 0.99]\* |
| Diabetes | 1.33 [1.01, 1.75]\* |
| Baseline CVP (mmHg) | 0.99 [0.97, 1.01] |
| CIT (hours) | 1.02 [0.97, 1.07] |
| Vena cava clamping time (minutes) | 0.99 [0.98, 0.99]\* |
| Baseline creatinine (10 μmol/L) | 0.97 [0.94, 0.99]\* |
| Piggyback | 0.87 [0.46, 1.62] |

*A HR > 1 increases the instantaneous risk being extubated considering the competing risk of dying. All results are expressed with 95% confidence intervals*

*\* Statistically significant*

**Table S6. Time to ICU discharge**

|  |  |
| --- | --- |
| **Variables** | **ICU discharge**  **(n=530)** |
| Fluid balance*\*\** | NA |
| Intraoperative phlebotomy | 1.14 [0.92, 1.41] |
| Age (years) | 0.99 [0.98, 1.00] |
| Gender (male) | 1.23 [1.01, 1.49]\* |
| Retransplantation | 0.73 [0.49, 1.07] |
| ALF | 0.53 [0.34, 0.84]\* |
| MELD | 0.98 [0.96, 0.99]\* |
| Diabetes | 1.02 [0.81, 1.30] |
| Baseline CVP (mmHg) | 0.99 [0.97, 1.00] |
| CIT (hours) | 0.99 [0.95, 1.02] |
| Vena cava clamping time (minutes) | 1.00 [0.99, 1.00] |
| Baseline hemoglobin (g/L) | 1.00 [0.99, 1.00] |
| Baseline creatinine (10 μmol/L) | 0.98 [0.96, 1.00] |
| Piggyback | 0.60 [0.36, 0.99]\* |

*\* Statistically significant*

*\*\* HR cannot be interpreted for the effect of fluid balance fitted as splines – please refer to figure S3. However, effect of fluid balance was significant from a likelihood ratio test with p = 0.005.*

*A HR > 1 increased the risk of being discharged.*

*HR = hazard ratio, NA = not applicable, ICU = intensive care unit, ALF = acute liver failure, CVP = central venous pressure, CIT = cold ischemia time*

**Figure S1. Effect of fluid balance on ICU discharge hazard**



*Effect must be estimated by visual analysis. Above 3 L of fluid balance, the confidence interval does not cross the null effect value anymore.*

**Figure S2. Effect of fluid balance on survival over time based on Schoenfeld residuals.**

****

Beta(t) for fluid balance

# **Appendix VII – Sensitivity analyses**

**Table S7. Statistically significant variables associated with AKI outcomes**

|  |  |  |
| --- | --- | --- |
| **Analyses** | **48-hour AKI** | **7-day AKI** |
| Primary analysis\* | Age, MELD, CIT | Age, MELD |
| Complete cases only | Age, MELD, CIT | -- |
| Missing ascites = 0 | Age, retransplantation, MELD, CIT | Age, MELD |
| AKI defined with creatinine values only | Age, MELD, CIT, baseline creatinine | CVP, clamping time |
| Fluid balance replaced by its components in the model\*\* | Age, MELD, CIT | Age |
| Death = AKI 3 | Age, retransplantation, MELD, CIT | Age, MELD |

*\* Primary analysis is the reported analysis in the manuscript.*

*\*\* Crystalloids, colloids, albumin, ascites and blood loss separated.*

*Age, MELD, CIT, CVP and clamping time were associated with an increased risk of AKI while retransplantation and baseline creatinine had protective effects in aforementioned models.*

*AKI = acute kidney injury, CIT = cold ischemia time, CVP = central venous pressure*

**Table S8. Statistically significant variables associated with creatinine clearances**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **30-day CrCl** | **180-day CrCl** | **365-day CrCl** |
| Primary analysis\* | Age, gender, diabetes, CVP, clamping time, baseline creatinine | Age, gender, CVP, baseline creatinine, baseline hemoglobin, starch exposure | Age, gender, CVP, baseline creatinine, baseline hemoglobin, starch exposure |
| Complete cases only | Fluid balance (polynomial), age, gender, baseline creatinine | Age, CVP, baseline creatinine, baseline hemoglobin, starch exposure | Age, gender, baseline creatinine, baseline hemoglobin, starch exposure |
| Missing ascites = 0 | Fluid balance (polynomial), age, gender, diabetes, CVP, clamping time, baseline creatinine | Age, gender, CVP, baseline creatinine, baseline hemoglobin, starch exposure | Age, gender, CVP, baseline creatinine, baseline hemoglobin, starch exposure |

*\* Primary analysis is the reported analysis in the manuscript.*

*Increased age, diabetes, higher baseline CVP, longer clamping time, a higher baseline creatinine and starch exposure were associated with lower CrCl. Being a male and a higher baseline hemoglobin concentration had protective effects.*

*A higher fluid balance was associated with a decreased 30-day CrCl up to 3 liters and with an increased 30-day CrCl thereafter (polynomial relationship) only in sensitivity analyses (-0.45\*FB + 0.16\*FB2).*

*CrCl = creatinine clearance, CVP = central venous pressure, FB = fluid balance*

**Table S9. Statistically significant variables associated with postoperative RRT and transfusions**

|  |  |  |
| --- | --- | --- |
| **Analyses** | **RRT** | **Postoperative RBC transfusions** |
| Primary analysis\* | Gender, MELD, CIT, baseline creatinine | MELD |
| Complete cases only | Gender, baseline creatinine | MELD |
| Missing ascites = 0 | Gender, MELD, CIT, baseline creatinine | MELD |

*\* Primary analysis is the reported analysis in the manuscript.*

*MELD, CIT and baseline creatinine were associated with an increased risk of RRT or transfusions, while being a male had a protective effect on RRT.*

*RRT = renal replacement therapy, RBC = red blood cells, CIT = cold ischemia time*

**Table S10. Statistically significant variables associated with extubation hazard, ICU discharge hazard et survival**

|  |  |  |  |
| --- | --- | --- | --- |
| **Analyses** | **Extubation hazard** | **ICU discharge hazard** | **Survival** |
| Primary analysis\* | Gender, MELD, ALF, clamping time, baseline creatinine | Fluid balance, gender, MELD, ALF, piggyback | Fluid balance, age, ALF |
| Complete cases only | Fluid balance (non-linear effect with interaction between fluid balance and phlebotomy), ALF | Fluid balance, MELD, ALF, baseline creatinine, piggyback | Fluid balance, age, Retransplantation, ALF, MELD |
| Missing ascites = 0 | Fluid balance (non-linear effect with interaction between fluid balance and phlebotomy), gender, MELD, ALF, vena cava clamping time | Fluid balance, MELD, ALF, baseline creatinine, piggyback | Fluid balance, age, ALF |

*\* Primary analysis is the reported analysis in the manuscript.*

*Fluid balance, MELD, a diagnosis of ALF, vena cava clamping time, the use of a piggyback technique and baseline creatinine were associated with either a decreased risk of being extubated or being discharged from ICU. Male gender had a protective effect. Fluid balance and ALF were also associated with an increased hazard of death.*

*ICU = intensive care unit, ALF = acute liver failure, CVP = central venous pressure*

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